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Intestinal permeability studies for piperaquine from dihydroartemisinin—piperaquine antimalarial product in the presence of lamivudine

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ABSTRACT

The study assessed the intestinal permeability of piperaquine (PQ) from dihydroartemisinin–piperaquine (DP) antimalarial in the presence of lamivudine (LMV). Excised tissues (duodenum and ileum) from New Zealand male albino rabbits (n = 2) were loaded with a suspension of DP equivalent to PQ (100 mg/ml) and LMV (100 mg/ml) and submerged in Tyrode solution (TS). DP suspension was similarly loaded as control. Sampling (5 ml) of TS was done post immersion of tissues and analyzed for PQ permeation using the high pressure liquid chromatographic system. LMV caused a significant increase in PQ permeation across the intestinal membranes. The rate constant (Ka) appearance in organ bath was (0.2457 ± 0.0040 hour^{-1} *vs.* 0.0367 ± 0.0008 hour^{-1}, p = 0.010) for duodenum and (0.2428 ± 0.0006 hour^{-1} *vs.* 0.0327 ± 0.0021 hour^{-1}, p = 0.008) for ileum. The Ka disappearance of PQ was (1.0121 ± 0.0013 hour^{-1} *vs.* 0.7600 ± 0.0008 hour^{-1}, p = 0.001) from duodenum and (1.0092 ± 0.0003 hour^{-1} *vs.* 0.7340 ± 0.0072 hour^{-1}, p = 0.017) from ileum. Area under the curve at 6 hours was (1.2868 ± 0.6725 µg.ml hour^{-1} *vs.* 3.3975 ± 0.3638 µg.ml hour^{-1}, p = 0.034) for duodenum and (0.7425 ± 0.0089 µg.ml hour^{-1} *vs.* 5.6603 ± 0.1073 µg.ml hour^{-1}, p = 0.013) for ileum. Co-loading of LMV with DP *ex vivo* caused significant uptake from the lumen but significant reduction in PQ permeation across the intestinal regions into the organ bath. This may be of biopharmaceutical implication requiring dosage adjustments.

INTRODUCTION

Ex-vivo studies involving stomach and intestinal segments have been extensively reported as a model for assessing the permeation or diffusion of drug molecules across absorptive membranes (Luo *et al*., 2013). This model serves as a preliminary evaluation of oral drug absorption and its mechanisms (Li *et al*., 2014). Orally administered pharmacologic agents are required to possess favorable absorption indices (Shugart and Benet, 2009). Several factors can affect absorption and consequently the bioavailability of drugs which include physicochemical and physiological considerations (Antunes *et al*., 2013). Most poorly water-soluble agents with demonstrable pharmacologic usefulness have been assessed for their therapeutic benefits (Gupta and Sehrawat, 2011). In recent times, real-life situation studies require the combination of information from different sources in experimental design to describe the *in vivo* scenario of drug applicability (Chapman and Wilson, 2013). The conditions under which a drug is evaluated for disintegration, dissolution, and absorption may preclude that which obtains when such agents are co-administered due to co-prescribing with other drugs (CDER, 2012).

Dihydroartemisinin–piperaquine (DP) is a cost-effective and well-prescribed drug for the treatment of uncomplicated *Plasmodium falciparum* malaria (Mori *et al*., 2014). DP has been recommended by the World Health Organization for the treatment of multi-drug resistant *P. falciparum* malaria. Malaria is a life-threatening parasites infection which can co-exist with Human Immunoviral (HIV) infection, thereby requiring the co-

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prescribing of antimalarial and antiretroviral agents (German *et al*., 2007; Uriel and Lewihwaite, 2011; Qureshi, 2016). Malaria has also been reported as the third leading cause of death in HIV positive individuals (Foca *et al*., 2012). Artemisinin-combination therapy has been reported to account for a significant proportion of clinically significant drug interactions with antiretroviral drugs (Oshikoya *et al*., 2014). In view of the arguments, lamivudine (LMV), a nucleoside reverse transcriptase inhibitor may be co-prescribed with piperaquine (PQ) in cases of co-morbidities (DHHS, 2017; Zhang *et al*., 2011).

A detailed review of possible concomitantly prescribed medications is required when selecting an antiretroviral, especially in cases of co-infections so as to avoid untoward drug-drug interactions (DDI) (Piscitelli and Galliciano, 2001). Integrase Strand Transfer Inhibitors (INSTIs) have the potential for decreased absorption from the gastrointestinal tract by polyvalent cations. It is recommended to give INSTIs at least 2 hours before or at least 6 hours after supplements containing polyvalent cations (Tseng, 2015). Similarly, LMV has been reported to cause pancreatitis resulting in increased intestinal motility. This may affect the absorption of concurrently administered drugs by a physiological mechanism.

This study aimed at assessing the effect of co-administration of LMV with DP on PQ permeation across the intestinal absorptive membrane.

MATERIALS AND METHODS

Materials

Pure reference sample of piperaquine phosphate and tinidazole was obtained from Central Research Laboratory, University of Lagos, Nigeria. High-Pressure Liquid Chromatographic (HPLC) grade acetonitrile and ammonium acetate were the products of Sigma Aldrich, Germany. Sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and sodium bicarbonate were the products of Sigma Aldrich Germany.

The drug products used were P-alaxin® and LMV tablets, products of Bliss GVC and Healthy Life Pharma, India, respectively. Distilled water was used throughout the study.

Preparation of standard solutions/physiologic solution

A powder weight of 50 mg reference standard PQ was taken and dissolved in 10 ml volumetric flask to prepare a 5 mg/ml stock solution. Serial dilutions of stock solution were made to produce graded concentrations in the range 1–100 mg/ml. The appropriate proportions of salts (i.e., sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium bicarbonate, and glucose) were dissolved to prepare 2.5 l of Tyrode solution (TS) according to standard TS preparation protocols.

Preparation of solutions of drugs/admixture of investigated drugs

Five tablets of each drug product (i.e., DP and LMV) were weighed and the respective mean weight obtained. The equivalent weights corresponding to the labeled claim of active ingredients were employed to calculate the amount of drug products (in powder) required to obtain a concentration of 100 mg/ml. The admixture of DP and LMV solutions were produced based on the doses for each drug per kg of rabbit weight.

Handling of animals

New Zealand albino male rabbits ($n = 2$) were employed for the study. Animals were fed with standard pellet diet for 1 week while allowing them to acclimatize with the environment. Animals were allowed access to water *ad libitum*. The animals were fasted for 2 days prior to the experiment. The protocol of the study was approved by the Faculty of Pharmacy, University of Uyo Ethics Committee on the Use of Laboratory Animals (UFP012). Good Laboratory Practice was observed throughout the study. The animals were handled based on the American Psychological Associations Guidelines for Ethical Conduct in the Care and Use of Non-human Animals in Research (AMA, 2010).

Preparation of tissues and organ bath set up

Organ bath containing 100 ml of TS was set up with a mechanical aerator in place. Animals were paralyzed by cervical dislocation and subsequently, the abdomen was exposed to ligate the duodenum (region after the stomach) and the ileum (region before the ileocecal junction). The tissues for the intestinal segments were cut into segments of 4 cm each.

Loading of tissues and sampling

One end of excised tissue was tied with silk thread while the investigated solution was loaded before tying the other end, based on animal body weight (i.e., 10.66 mg of PQ/kg and 4 mg of LMV/kg). Sampling (5 ml) was taken at 0, 0.5, 1, 2, 4, and 6 hours with the replacement of equal amount of fresh TS solution. The samples were filtered using 0.45 µm Acrodisc syringe filter and filtrate stored in ultra-freezer at −20°C pending analysis.

High-pressure liquid chromatographic analysis

Samples were analyzed on a Chemstation HPLC system equipped with a UV detector. A C8 Zorbact XDB reverse phase (150 × 4.6 mm, 4.6 µm) column was employed for the chromatographic analysis. The mobile phase consisted of acetonitrile and 10 mM ammonium acetate (70:30, $\%^{v}/_{v}$) while the wavelength of detection and flow rate were 220 nm and 0.7 ml/minute, respectively. The injection volume was 1 µl and the column was maintained at 20°C throughout the analysis.

Pharmacokinetic and statistical analysis

The deduced PQ concentration of samples was computed and analyzed with APK pharmacokinetic software version 13 (Rxkinetics, USA). Significant differences between the pharmacokinetic parameters derived for treatments were compared and analyzed using Paired *T*-test employing SPSS version 20 (IBM, USA) and the significance level was set at alpha = 5% (i.e., $p = 0.05$) for all comparisons.

RESULTS

A representative chromatograph of the PQ is presented in Figure 1. Peaks for the concentration of PQ and IS were clearly portrayed in the chromatographs with peaks for PQ and IS at about 4.3 and 2.2 minutes, respectively. PQ concentration time curves for the experimental conditions are presented in Figure 2. LMV caused a decrease in the permeation of PQ in both intestinal regions. The effective permeability coefficient (P_{eff}) for PQ

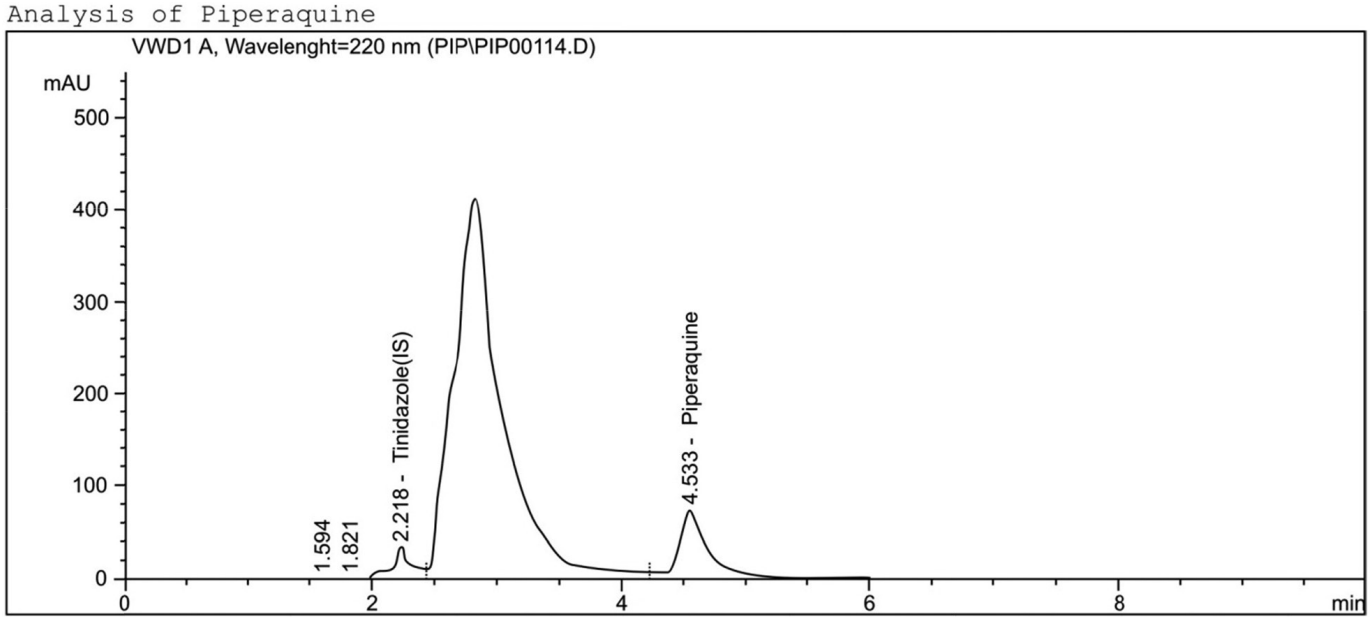

Figure 1. Representative chromatograph of the sample from intestinal perfusion containing PQ.

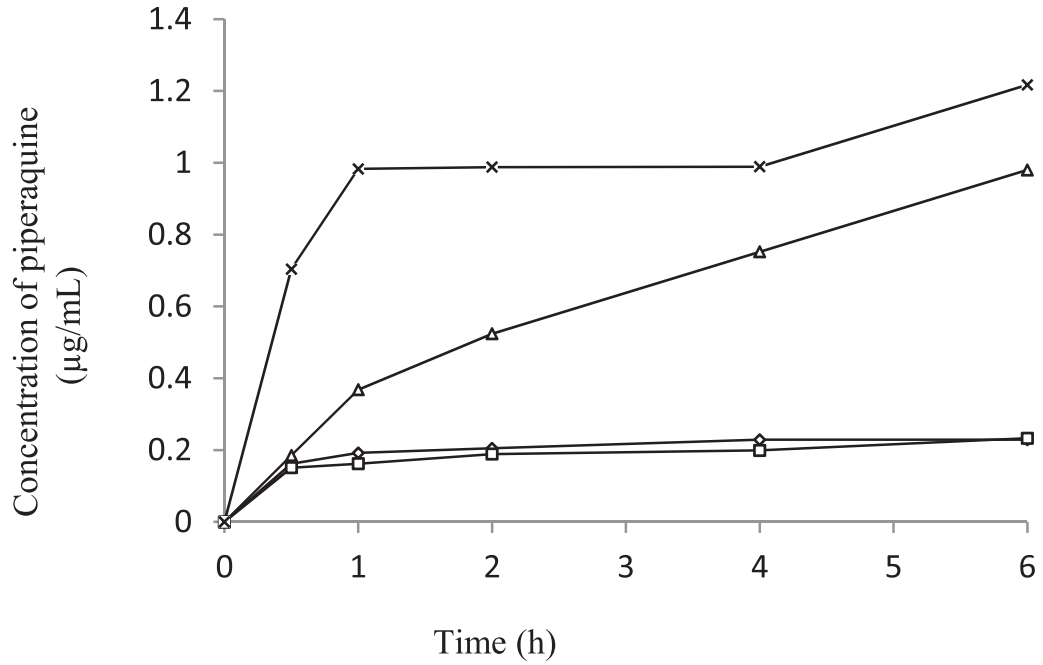

Figure 2. Permeation of PQ across duodenal/ileal intestinal epithelia (xID = DP alone in ileum, □IDL = DP alone in ileum, ΔDD = DP alone in duodenum, and ◊DDL = DP + LMV in duodenum).

appearance in organ bath was higher in the test than the control in the duodenal set-up. Similarly, LMV caused a higher P_{eff} for the appearance of PQ in the organ bath for the ileal set-up ($p < 0.05$). In the luminal environment, the P_{eff} disappearance for PQ revealed higher permeation of the analyte in the test than their respective controls ($p < 0.05$). No difference in the regional P_{eff} of PQ for the test and the controls as revealed in Figure 3. The P_{eff} appearance and P_{eff} disappearance for PQ are illustrated in Figure 3.The area under the curve for 2 hours (AUC_2) post immersion in the test was lower than its control value in the duodenum set-up. Similarly, a lower AUC_2 value was observed for the test in the ileal experiment. Table 1 presents some pharmacokinetic indices for PQ transport across the intestinal barrier. The test revealed that there was no significant difference in the oral absorption rate of PQ compared with the control in the duodenal set-up ($p = 0.130$) while there was higher rate due to LMV in the ileal set-up ($p = 0.049$). The C_{max} in the duodenal set-up showed a lower value than its control ($p = 0.015$). Similarly, LMV revealed lower C_{max} value for PQ in organ bath in the ileal set-up ($p = 0.009$).

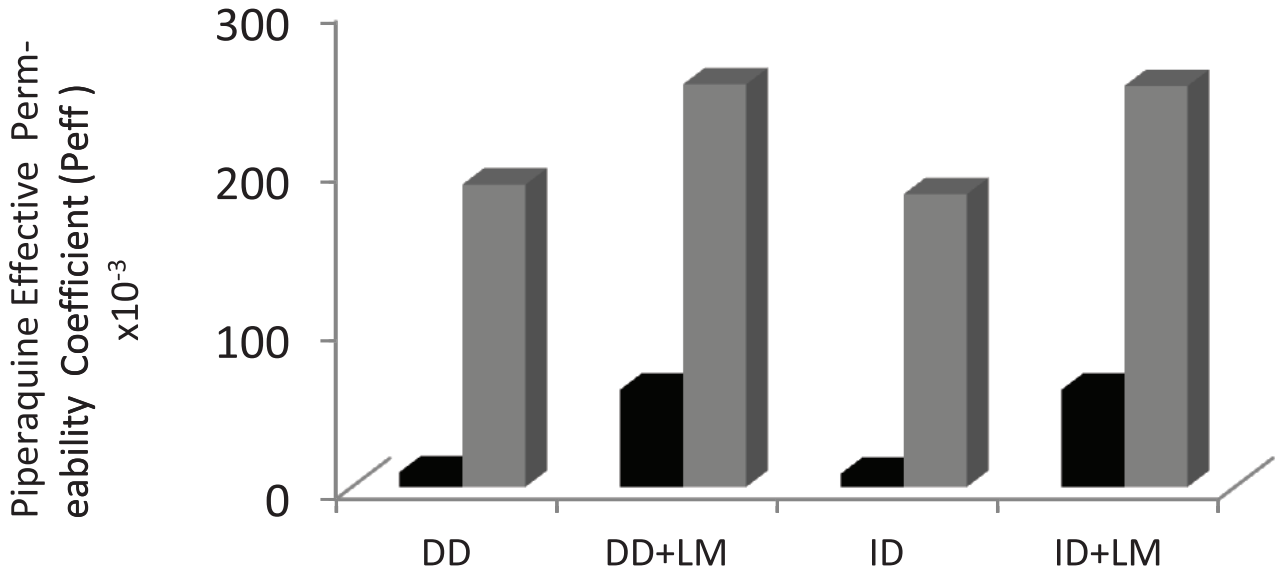

Figure 3. Effective permeability coefficient (P_{eff}) of PQ calculated for ■appearance in an organ bath and □disappearance from the lumen, (DD = DP alone in the duodenum, DD + LM = DP with LMV in the duodenum, ID = DP alone in ileum, and ID + LMV= DP with LMV in ileum).

DISCUSSION

The oral route is the major and preferred route of drug delivery for the treatment of chronic diseases due to convenience and improved patient safety (Verma *et al*., 2010). This study, therefore, was designed to assess the oral delivery of PQ across the intestinal region in the presence of another simultaneously administered drug. The importance of the study was to highlight the pharmacokinetic implications of co-prescribing medications in co-morbidities. The subject of DDI following orally administered therapy is gaining relevance in recent years as one drug is often co-prescribed with others as studied in this work (Bazzoni *et al*., 2015). PQ investigated in this study is an important partner in DP combination for malarial treatment strategies (Moore *et al*., 2008). There is a paucity of detailed preclinical and clinical pharmacokinetic data to link PQ intestinal absorption with its consequent serum concentration alongside cases of efficacy or safety (Tarning *et al*., 2008). LMV was selected for this study as it is the first nucleoside analog registered for the treatment of chronic hepatitis B (Henry *et al*., 2012), prevention of perinatal hepatitis B viral infections (Margolis *et al*., 1995), and transmission of HIV (Caudros *et al*., 2011; Mave *et al*., 2014). This study, therefore, seeks to assess the permeation or diffusion of PQ across intestinal epithelium in the co-formulated state (i.e., DP) on co-administration with LMV.

This preliminary *ex vivo* method was employed for the study because of the inherent advantages. These include simplicity and convenience of operation, as the experimental conditions and environment are easy to control alongside the obtainment of reproducible outcomes. The test set up revealed PQ disappearance from intestinal lumen producing a striking reduction in values compared with their control. It appeared, therefore, that LMV caused mobilization of PQ from the luminal space into the epithelial environment, adjudging by the ka for PQ disappearance value. This explanation is expected to hold for the high values of ka appearance in TS but negated by the low AUC and C_{max} values when compared with their respective controls.

AUC values of PQ for 2 and 6 hours post immersion were to assess the promptness and extent of PQ permeation, respectively. Malaria being an acute febrile illness requires prompt blood level antimalarial agents; hence, the co-formulation design of dihydroartemisinin with PQ in DHA. Dihydroartemisinin, on the other hand, has a short half-life of 2 hours (Rijken, 2011). The extent of PQ diffusion will reinforce the rapid action required from the partner drug. Previous researchers have highlighted the low

Table 1. Kinetics of PQ release for the media conditions.

Parameters		Media conditions			
		Duodenum		Ileum	
		DP and LMV	DP alone	DP and LMV	DP alone
Ka (hour^{-1})		0.0153 ± 0.0032	0.0023 ± 0.0002	0.0153 ± 0.0008	0.0020 ± 0.0003
(C_{max}) ± SEM		0.2240 ± 0.0015	0.9800 ± 0.0025	0.2440 ± 0.0023	1.2170 ± 0.0070
R^2 values	Zero	0.9438	0.4638	0.5169	0.5645
	First	0.2497	0.1017	0.0047	0.0757
	Second	0.1776	0.0258	0.0135	0.0108

NB: C_{max} and SEM represent the maximum concentration attained in an organ bath and standard error of the mean of treatments, DP and LMV represent dihydroartemisinin-piperaquine and lamivudine, respectively. Ka represents the absorption rate constant.

oral bioavailability of PQ in different population pharmacokinetic studies (Ashley *et al*., 2004). The success of this co-formulation on simultaneous administration with LMV will depend on the DDI at the absorptive site. AUC_2 and AUC_6 were significantly lower than their respective control values, an indication of DDI at the intestinal uptake/permeation level. This significant reduction in the overall drug permeation becomes noteworthy more so as LMV mobilized significantly PQ uptake. The evident increase in Ka values and reduction in AUC values due to LMV is an indication of "trapping" of PQ within the membrane or reverse transport of PQ back into the epithelium from the TS.

LMV permeates through the intestinal tissues by passive diffusion or actively transported by uptake transporters termed the solute carrier superfamily including (SLC22A1, SLC22A2, and SLC22A3) and has a high oral bioavailability and high volume of distribution (Whirl-Carrillo *et al*., 2012). It is also actively transported out of the cell by efflux transporters ABCB1, ABCC1, ABCC2, ABCC4, and ABCG2. In its monophosphate form, it is transported out of the cell by ABCG2 (Whirl-Carrillo *et al*., 2012). It has been reported that PQ, like LMV, is majorly absorbed by passive diffusion (Yuen *et al*., 1995). PQ has an intrinsic poor aqueous solubility that constitutes major limitations to its successful oral drug delivery (Sharma *et al*., 2016). The co-administration of LMV with PQ sharing the same transepithelial transport mechanism (i.e., passive diffusion) has been shown to reduce the permeation of PQ in this *ex vivo* experiment. A rapid decline in the susceptibility of *P. falciparum* to DP has been reported recently and this may not be unconnected with the sub-optimal permeability of the actives in DP, especially PQ (Thanh *et al*., 2017).

LMV has been reported to cause pancreatitis, infrequently in adults but more common in pediatric patients (Suzuki *et al*., 2014). This physiological influence alongside widely reported intestinal membrane irritation may be responsible for membrane permeability property changes leading to altered intestinal permeation of PQ. Other major reported intestinal side effects are nausea, vomiting, and diarrhea (Neuman *et al*., 2012). The co-administration of LMV with other drugs (i.e., antimalarial agents which have co-morbidity with HIV or HBV infections) will require a proper assessment to optimize therapy.

This study also revealed a significant reduction in PQ permeation across duodenal epithelium in the presence of LMV as revealed by the AUC values (Table 2). Researchers have recommended spacing out the time for the administration of drugs such as 3-hydroxyl-3-methylglutaryl coenzyme A reductase inhibitors with LMV (Bader and Kober, 2010) in order to prevent DDIs. Similarly, there is the need to assess the effect of LMV on the bioavailability of PQ in DP on concurrent administration in the light of the recurrent antimalarial resistance reported across the globe.

Table 2. Area under curve (AUC) at 2 and 6 hours for the intestinal regions and media conditions.

Media condition	AUC^2 (μg.minute.ml^{-1})		AUC^6 (μg.minute.ml^{-1})	
	Duodenum	Ileum	Duodenum	Ileum
Test	0.3447 ± 0.0172	0.3036 ± 0.0120	1.2868 ± 0.6725	0.7425 ± 0.0089
Control	0.6198 ± 0.0083	1.5408 ± 0.4275	3.3975 ± 0.3638	5.6603 ± 0.1073

NB: AUC_2 and AUC_6 represent area under curve for 0–2 hours and 0–6 hours, respectively.

The P_{eff} of LMV is in the range of drugs with high intestinal permeability indicating that LMV readily crosses the intestine. Such is the nature of drugs belonging to BCS Class 1. The drug PQ has been reported to be of low bioavailability as shown in passive diffusion across intestinal epithelium and this is dependent on many pharmacokinetic characteristics such as lipophilicity, molecular weight, and hydrophobic bonding. The combination of the two drugs will mean that LMV suppresses the passive diffusion of the poorly water-soluble PQ. The absorption of drugs via the oral route is always under examination due to the fact that unhindered diffusion and consequent good bioavailability indicates that the drug will reach systematic circulation (Hetal *et al*., 2010).

In an *in vitro* study previously reported by Awofisayo *et al*. (2018), there was no chemical interaction between LMV and any of the actives in DP using Fourier transform infrared spectroscopic analysis and assessment of troughs and peaks observed. It, therefore, suffices that the DDI between LMV and DP involves a physiological mechanism (i.e., membrane absorption characteristics alteration).

CONCLUSION

This study revealed that LMV reduced the intestinal permeability of PQ from DP on co-administration. This intestinal permeability has been demonstrated in the duodenum and ileum which shows the cumulative influence of LM on PQ. The novelty of this work is highlighted in the recommendation of spacing apart of drug dosing in the cases of co-prescribing of the investigated drugs. This will help against sub-optimal therapeutic concentrations of PQ in antimalarial therapy leading to parasitic resistance.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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